

# Review on Breast cancer

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## Abstract:

Breast cancer (BC) is the most frequently diagnosed cancer in women worldwide with more than 2 million new cases in 2020. Its incidence and death rates have increased over the last three decades due to the change in risk factor profiles, better cancer registration, and cancer detection. The number of risk factors of BC is significant and includes both the modifiable factors and non-modifiable factors. Currently, about 80% of patients with BC are individuals aged >50. Survival depends on both stage and molecular subtype. Invasive BCs comprise wide spectrum tumors that show a variation concerning their clinical presentation, behavior, and morphology. Based on mRNA gene expression levels, BC can be divided into molecular subtypes (Luminal A, Luminal B, HER2-enriched, and basal-like). The molecular subtypes provide insights into new treatment strategies and patient stratifications that impact the management of BC patients. The eighth edition of TNM classification outlines a new staging system for BC that, in addition to anatomical features, acknowledges biological factors. Treatment of breast cancer is complex and involves a combination of different modalities including surgery, radiotherapy, chemotherapy, hormonal therapy, or biological therapies delivered in diverse sequences.

**Keywords:** breast cancer, epidemiology, risk factors, classification, diagnosis, prognosis, marker, treatment.

## Introduction

Being characterized by six major hallmarks, carcinogenesis might occur in every cell, tissue, and organ, leading to the pathological alternations that result in a vast number of cancers. The major mechanisms that enable its progression include evasion of apoptosis, limitless capacity to divide, enhanced angiogenesis, resistance to anti-growth signals and induction of own growth signals, as well as the capacity to metastasize [1]. Carcinogenesis is a multifactorial process that is primarily stimulated by both—genetic predispositions and environmental causes. The number of cancer-related deaths is disturbingly increasing every year ranking them as one of the major causes of death worldwide. Even though a significant number of cancers do not always need to result in death, they significantly lower the quality of life and require larger costs in general.

Breast cancer is currently one of the most prevalently diagnosed cancers and the 5th cause of cancer-related deaths with an estimated number of 2.3 million new cases worldwide according to the GLOBOCAN 2020 data [2]. Deaths due to breast cancer are more prevalently reported (an incidence rate approximately 88% higher) in transitioning countries (Melanesia, Western Africa, Micronesia/Polynesia, and the Caribbean) compared to the transitioned ones (Australia/New Zealand, Western Europe, Northern America, and Northern Europe). Several procedures such as preventive behaviors in general as well as screening programs are crucial regarding a possible minimization of breast cancer incidence rate and the implementation of early

treatment. Currently, it is the Breast Health Global Initiative (BHGI) that is responsible for the preparation of proper guidelines and the approaches to provide the most sufficient breast cancer control worldwide [3]. In this review article, we have focused on the female breast cancer specifically since as abovementioned, it currently constitutes the most prevalent cancer amongst females.



Fig:1. Breast cancer

## Epidemiology of Breast cancer

According to the WHO, malignant neoplasms are the greatest worldwide burden for women, estimated at 107.8 million Disability-Adjusted Life Years (DALYs), of which 19.6 million DALYs are due to breast cancer. . Breast cancer is the most frequently diagnosed cancer in women

worldwide with 2.26 million [95% UI, 2.24–2.79 million] new cases in 2020 [4]. In the United States, breast cancer alone is expected to account for 29% of all new cancers in women. The 2018 GLOBOCAN data shows that age-standardized incidence rates (ASIR) of breast cancer are strongly and positively associated with the Human Development Index (HDI). According to 2020 data, the ASIR was the highest in very high HDI countries (75.6 per 100,000) while it was more than 200% lower in medium and low HDI countries (27.8 per 100,000 and 36.1 per 100,000 respectively).

Breast cancer incidence and death rates have increased over the last three decades. Between 1990 and 2016 breast cancer incidence has more than doubled in 60/102 countries (e.g., Afghanistan, Philippines, Brazil, Argentina), whereas deaths have doubled in 43/102 countries (e.g., Yemen, Paraguay, Libya, Saudi Arabia) [5]. Current projections indicate that by 2030 the worldwide number of new cases diagnosed reach 2.7 million annually, while the number of deaths 0.87 million [6]. In low- and medium-income countries, the breast cancer incidence is expected to increase further due to the westernization of lifestyles (e.g., delayed pregnancies, reduced breastfeeding, low age at menarche, lack of physical activity, and poor diet), better cancer registration, and cancer detection.

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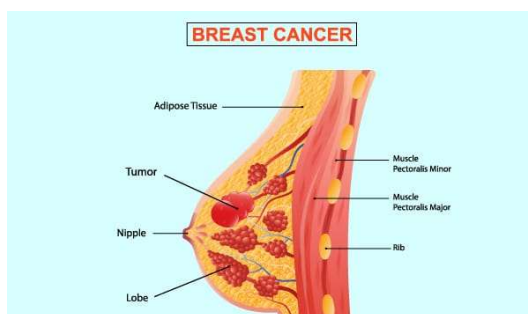


FIG:2.Epidemiology of breast cancer

Besides being the most common, breast cancer is also the leading cause of cancer death in women worldwide. Globally, breast cancer was responsible for 684,996 deaths [95% UI, 675,493–694,633] at an age-adjusted rate of 13.6/100,000. Although incidence rates were the highest in developed regions, the countries in Asia and Africa shared 63% of total deaths in 2020. Most women who develop breast cancer in a high-income country will survive; the opposite is true for women in most low-income and many middle-income countries [7].

In 2020 breast cancer mortality-to-incidence ratio (MIR) as a representative indicator of 5-year survival rates was 0.30 globally. Taking into consideration the clinical extent of

breast cancer, in locations with developed health care (Hong-Kong, Singapore, Turkey) the 5-year survival was 89.6% for localized and 75.4% for regional cancer. In less developed countries (Costa Rica, India, Philippines, Saudi Arabia, Thailand) the survival rates were 76.3% and 47.4% for localized and regional breast cancer respectively [8].

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#### Risk factors for developing breast cancer among women

- **Personal history of breast cancer**

An increased risk of breast cancer recurrence exists in women who have previously experienced it. The second breast cancer may appear in the same breast as the first one or in a different breast. Although the majority of women who have ductal carcinoma in situ or lobular carcinoma in situ breast cancers do not recur, these women are at an increased risk of doing so.

- **Breast and other types of cancer in the family history**

The presence of breast cancer in one or more close blood relatives indicates that the disease runs in the family. More breast cancer cases than one might anticipate randomly occur in some families. It can be difficult to determine whether a family's history of cancer is the result of coincidence, a common lifestyle, genes passed down from parents to children, or a combination of these factors.

- **Mutations in the BRCA gene**

An altered gene is referred to as a genetic mutation. Certain types of cancer may be more likely to develop as a result of some gene changes. A parent can pass on inherited gene mutations to their offspring. Only a small percentage of breast cancers (roughly 5%–10%) are brought on by inherited gene mutations. Normal human physiology includes both BRCA1 and BRCA2, which are breast cancer genes. As a result of what seems to be their involvement in regulating the growth of cancer cells, these genes are known as tumor suppressors. BRCA1 or BRCA2 gene mutations may cause them to lose their ability to regulate the development of cancer. Rarely occur these mutations.

Roughly 1 in 500 people experience them. A mutated BRCA gene can be inherited by both men and women from either their mother or father. Children of those who carry the gene mutation may also inherit it. A child has a 50% chance of inheriting the gene mutation if 1 of the 2 copies of the BRCA gene has the mutation in 1 or both parents. A child also has a 50% chance of not inheriting the gene mutation, according to this.[10] According to studies, women who inherit BRCA1 or BRCA2 gene mutations have an 85% lifetime risk of developing breast cancer. Additionally, compared to other women, those who carry these inherited mutations are at an increased risk of developing breast cancer earlier in life. Breast cancer in both breasts is more likely to strike women who have the BRCA gene mutation. They are more likely to get cancer in the other breast if they have cancer in 1 breast. Ovarian cancer can strike a woman at any age if she carries a BRCA gene mutation.

- **Large breasts**

Compared to fatty tissue, dense breasts have more milk ducts, glands, and connective tissue. Breast density is a genetic trait. Compared to women with little or no dense breast tissue, women with dense breast tissue have a higher risk of developing breast cancer. Breast density can only be detected by a mammogram, but dense breasts also make the image more difficult to interpret. On a mammogram, dense tissue appears white, like tumors, while fatty tissue appears dark, concealing a tumor.

- **The late menopause**

The body's level of hormones, primarily estrogen and progesterone, begins to decline as the ovaries stop producing them, resulting in menopause. A woman's menstrual cycle is stopped as a result of this. Your cells are exposed to estrogen and other hormones for a longer period if you enter menopause later in life. This raises the possibility of breast cancer. Likewise, breast tissue is exposed to estrogen and other hormones for a shorter period when menopause occurs earlier in life. A lower risk of breast cancer is associated with early menopause.

- **Whether there are late or no pregnancies**

Breast cells' exposure to circulating estrogen is halted during pregnancy. It also reduces the overall number of menstrual cycles a woman experiences throughout her lifetime. A woman's risk of breast cancer is marginally higher than it is for a woman who has at least one full-term pregnancy before the age of 30. Reduced risk of breast cancer is associated with early pregnancy. A woman is more protected from breast cancer the more children she has. Breast cancer risk is increased if a woman never conceives.

- **Hormonal replacement treatment**

According to the Women's Health Initiative (WHI) study, estrogen alone increased breast cancer risk by about 1% per year and combined hormone replacement therapy (HRT)

increased risk by about 8% per year. The study also discovered that, in comparison to a placebo, the risk increased even with relatively brief use of combined HRT. After stopping HRT for a few years, the higher risk seems to be gone. The WHI study also revealed that, among Canadian women aged 50 to 69, there was a notable decline in the number of new cases of breast cancer between 2002 and 2004. The use of combined HRT decreased at the same time as this drop. Other nations around the world, such as the United States, Australia, Germany, the Netherlands, Switzerland, and Norway, have also noticed this trend. The risks associated with the long-term use of combined HRT are now thought to outweigh the advantages.

- **Being overweight**

In post-menopausal women, obesity increases the risk of developing breast cancer. According to studies, women with a body mass index or higher who have never used HRT are 2.5 times more likely to develop breast cancer than those with a body mass index of 22.6 or lower. In particular, estrogens from the ovaries play a significant role in breast cancer. Many breast cancer risk factors are thought to be caused by the cumulative estrogen dose that the breast tissue absorbs over time. The majority of the body's estrogen is produced by the ovaries, but after menopause, fat tissue only produces a small amount of estrogen. A higher estrogen level can result from having more fat tissue, which raises the risk of breast cancer.



FIG: 3. Symptoms of breast cancer

- **Estrogen**

Breast cancer risk is linked to estrogens, both endogenous and exogenous. In premenopausal women, the ovary typically produces endogenous estrogen, and ovarian removal can lower the risk of breast cancer. HRT and oral contraceptives are the main exogenous estrogen sources. Since the 1960s, oral contraceptives have been extensively used, and their formulations have been improved to minimize side effects. The odd ratio is still higher than 1.5 for Iranian and African American female populations, though. Oral contraceptives do not, however, raise the risk of breast cancer in women who stop using them for more than 10 years. For menopausal or postmenopausal women, HRT entails the administration of exogenous estrogen or other

hormones. The use of HRT can raise the risk of breast cancer, according to several studies. According to the Million Women Study in the UK, there is a 1.66 relative risk between those who currently use HRT and those who have never used it. A cohort study of 22,929 Asian women found that after using HRT for 4 and 8 years, respectively, hazard ratios (HRs) of 1.48 and 1.95 were found. After 2 years of stopping HRT, it has been demonstrated that the risk of breast cancer significantly declines. With a 3.6 HR for a new breast tumor, the recurrence rate is also high among breast cancer survivors who take HRT. Since the negative effects of HRT were revealed in 2003 based on the WHI randomized controlled trial, there has been a 7% decrease in the incidence rate of breast cancer in America.

### Biology-based breast cancer prevention

To enhance the quality of life for breast cancer patients, biological prevention, primarily known as monoclonal antibodies for the disease, has recently been developed. These monoclonal antibodies have human epidermal growth factor receptor 2 (HER2) as one of their primary targets. The HER2 protein is overexpressed or the HER2 gene is amplified in about 20% to 30% of all breast cancer cases. The first HER2-targeted medication to receive FDA approval is trastuzumab (Herceptin), a recombinant humanized monoclonal antibody. It can directly interact with the C-terminal region of domain IV in the extracellular region of HER2. Trastuzumab's anti-tumor mechanism has not yet been fully understood. Trastuzumab may inhibit the growth and proliferation of cancer cells through several possible mechanisms, including activating the immune system against cancer cells through an effect known as antibody-dependent cell-mediated cytotoxicity, inhibiting the MAPK and PI3K/Akt pathways, and enlisting ubiquitin to internalize and degrade HER2. With an objective response rate of 26%, trastuzumab was initially used to treat metastatic breast cancer. [11].

Trastuzumab interacts favorably with other anti-tumor medications, including nimotuzumab, carboplatin, 4-hydroxycyclophosphamide, docetaxel, and vinorelbine, according to in vitro studies. According to the HERA and TRAIN trials, chemotherapy given in combination with adjuvant trastuzumab for a year can prolong disease-free survival in HER2+ breast cancer patients (HR = 0.76). Trastuzumab plus docetaxel was shown to be more effective than docetaxel alone in treating HER2-positive metastatic breast cancer, with an objective response rate of 50% versus 32%, in a randomized phase II trial carried out by Marty. Patients receiving trastuzumab, however, also experienced adverse effects like congestive heart failure and a decline in their left ventricular ejection fraction.

### Pathology of breast cancer

Ninety-five percent of breast cancers are carcinomas, i.e., they arise from breast epithelial elements. Breast cancers are divided into 2 major types, in situ carcinomas and invasive (or infiltrating) carcinomas. The in situ carcinomas may arise in either ductal or lobular epithelium, but remain confined there, with no invasion of the underlying basement membrane that would consist extension beyond epithelial boundaries.

When there is extension of the ductal or lobular malignancy beyond the basement membrane that constitutes the epithelial border, then the malignancy is considered invasive (or infiltrating) ductal or lobular carcinoma.

### RELATIONSHIP OF BENIGN BREAST DISEASE WITH BREAST CANCER

This is an issue of great concern for patients, physicians and insurance companies alike, as there are conditions that confer no risk of malignancy and others that definitely confer increased risk. Breast biopsies conferring no significantly increased risk for malignancy include any lesion with non-proliferative change.<sup>25,26</sup> These include duct ectasia and simple fibroadenomas, benign solid tumors containing glandular as well as fibrous tissue. The latter is usually single but may be multiple. Solitary papillomas are also benign lesions conferring no increased risk of future malignancy, despite the fact that they are often (in 21 of 24 women in a single study<sup>27</sup>) with sanguineous or serosanguineous nipple discharge. Fibrocystic change (cysts and/or fibrous tissue without symptoms) or fibrocystic disease (fibrocystic changes occurring in conjunction with pain, nipple discharge, or a degree of lumpiness sufficient to cause suspicion of cancer) does not carry increased risk for cancer (other than the potential for missing a malignant mass).<sup>28</sup> Some clinicians differentiate fibrocystic change or disease into those of hyperplasia, adenosis, and cystic change because of their differentiation into age distributions. Hyperplasia characteristically occurs in women in their 20s, often with upper outer quadrant breast pain and an indurated axillary tail, as a result of stromal proliferation. Women in their 30s present with solitary or multiple breast nodules 2–10 mm in size, as a result of proliferation of glandular cells.

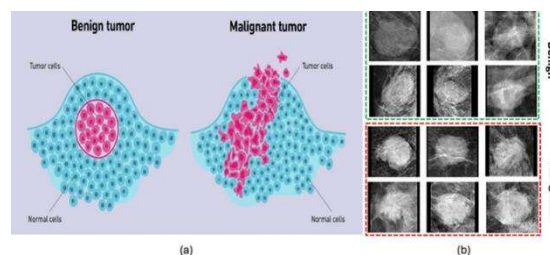


FIG:3.Benign and Malignant tumor



Women in their 30s and 40s present with solitary or multiple cysts. Acute enlargement of cysts may cause pain, and because breast ducts are usually patent, nipple discharge is common with the discharge varying in color from pale green to brown.<sup>29</sup> Conditions with increased risk of malignancy include ductal hyperplasia without atypia. This is the most commonly encountered breast biopsy result that is definitely associated with increased risk of future development of breast cancer and confers a 2-fold increased risk. The number, size and shape of epithelial cells lining the basement membrane of ducts are increased, but the histology does not fulfill criteria for malignancy. The loss of expression of transforming growth factor-receptor II in the affected epithelial cells is associated with an increased risk of invasive breast cancer.<sup>30</sup> A number of other benign lesions also confer a roughly 2-fold increased risk for development of breast cancer. These include sclerosing adenosis, where lobular tissue undergoes hyperplastic change with increased fibrous tissue and interspersed glandular cells, diffuse papillomatosis which is the formation of multiple papillomas, and fibroadenomas with proliferative disease, which are tumors that contain cysts greater than 3 mm in diameter, with sclerosing adenosis, epithelial calcification, or papillary apocrine change. Radial scars are benign breast lesions of uncertain pathogenesis, which are usually discovered incidentally when a breast mass is removed for other reasons. Radial scars are characterized by a fibroelastic core from which ducts and lobules radiate.<sup>31</sup> Atypical hyperplasia of either ductal or lobular cells, where the cells are uniform but have lost their apical-basal cellular orientation, confers a 4-fold increased risk unless there is also a family history of 1 or more first-degree relatives with breast cancer, where the risk increases to 6-fold.<sup>[12]</sup>

## DETECTION OF BREAST CANCER

Breast cancer detection involves regular screenings like mammograms, clinical exams, and self-awareness for changes, alongside advanced imaging (ultrasound, MRI) and definitive biopsies for suspicious areas, all guided by personalized risk assessment with a doctor for optimal early diagnosis and treatment.

### Screening & Early Detection Methods

- Mammogram: The primary screening tool, an X-ray that can find cancers years before they're felt, often followed by diagnostic mammograms for clearer views.
- Breast Self-Awareness: Knowing your breasts and checking for new lumps, skin changes (dimpling, redness), nipple inversion, or discharge, and reporting any changes to a doctor.
- Clinical Breast Exam (CBE): Performed by a healthcare professional during checkups.
- Breast Ultrasound: Uses sound waves to determine if a lump is solid or a cyst.
- Breast MRI: Uses magnets and radio waves for detailed images, often for high-risk individuals or to assess cancer extent. <sup>[13]</sup>.

### Diagnostic Confirmation

- Biopsy: The only definitive way to diagnose cancer, involving removing a tissue or fluid sample for microscopic analysis.

## DIAGNOSING BREAST CANCER: THE BIOPSY

Axillary recurrence or tumor involvement in internal mammary or supraclavicular lymph nodes always indicates a poor prognosis.<sup>39</sup> Sentinel lymph node biopsy is a biopsy of level I axillary lymph nodes. It has a positive predictive value approaching 100%, with a sensitivity of 89% and a specificity of 100%.<sup>40</sup> Three percent of positive sentinel nodes, however, are found in non-axillary regions. There appears to be a 15% incidence of "skip" metastases, defined as metastases to level II and III axillary nodes without involvement of level I nodes.<sup>38</sup> Thus, the cost of performing sentinel node biopsy alone is reflected in a study in which the 10 year survival rate of 85% for stage I breast cancer patients who have full axillary dissection falls to 66% when axillary dissection was not performed.<sup>41</sup> A more complete discussion of sentinel lymph node biopsy can be found in a recent issue of this journal.<sup>42</sup> High nuclear grade (high nucleus-to-cytoplasmic ratio), high mitotic index and poorly differentiated all connote poor prognosis (see Table 3 for the most commonly used and useful histopathologic scoring system). Infiltrating ductal carcinoma is by far the most common type of invasive breast cancer, with relatively poorer survival. (See Figures 1 and 2) Tubular, medullary, mucinous, and papillary cancers have a more favorable prognosis, but account for only 6% of invasive cancers.<sup>39</sup> Peritumoral lymphatic and blood vessel invasion connotes a much poorer prognosis.<sup>[14]</sup>

Estrogen and/or progesterone receptor positive tumors have a better prognosis and a better response to hormone treatment than receptor-negative tumors. Flow cytometry measures DNA Index (or DNA content), with diploid cancer cells (normal DNA content, DNA index of 1) having a better prognosis than those with aneuploidy.<sup>43</sup> S-phase fraction refers to the number of cells actively synthesizing DNA. Tumors with high S-phase cells have a poorer differentiation and poorer prognosis.<sup>44</sup> Tumor marker CA 15-3 is increased in many women with metastatic breast cancer. HER-2/neu oncoprotein (also called c-erbB 2) is associated with shorter survival, shorter time-to-relapse, and an overall worse prognosis.<sup>1</sup> This tumor marker is especially important with the introduction of trastuzumab for treatment. CA 27.29 is the

first FDA-approved (in June 1996) blood test for breast cancer recurrence.

## SURGICAL TREATMENT OF BREAST CANCER

The Consensus Development Conference on the Treatment of Early-Stage Breast Cancer (June 1990, NCI) has concluded that breast conservation treatment is an appropriate method of primary therapy for the majority of women with Stage I and Stage II breast cancers.

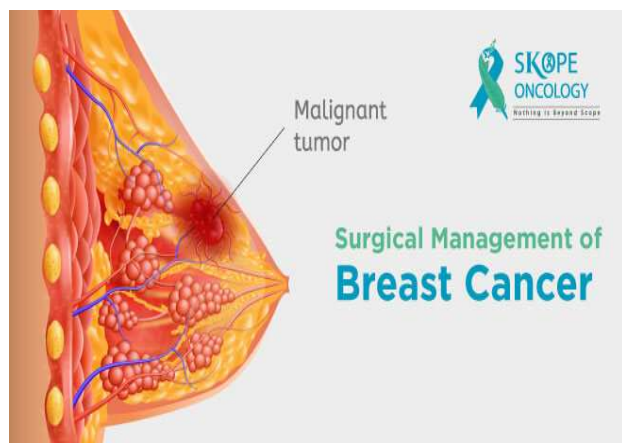


FIG:4. Surgical treatment of breast cancer

This treatment is preferable in many cases because it provides survival equivalent to total mastectomy and axillary dissection while preserving the breast.<sup>80</sup> Subsequent studies have confirmed that there is no difference in long-term survival between surgical removal of the breast (mastectomy) and excision of the tumor mass and radiation therapy to residual breast tissue (breast conservation therapy).<sup>81–83</sup> Breast-conserving surgery includes lumpectomy, re-excision, partial mastectomy, quadrantectomy, segmental excision, and wide excision.<sup>[15]</sup>

Axillary lymph nodes are removed for evaluation through a separate incision. The most common breast-removal procedure is a modified-radical mastectomy, which involves making an elliptical incision around an area including the nipple and biopsy scar, removing that section, and tunneling under the remaining skin to remove the breast tissue and some lymph nodes. Radical mastectomy, which removes the entire breast, chest wall muscles, and all axillary lymph nodes, is rarely done today because it offers no survival advantage over a modified radical mastectomy. A simple, or total mastectomy, removes the entire breast but none of the axillary lymph nodes. This is usually done for women with DCIS, or prophylactically for women at especially high risk for developing breast cancer. A newer procedure is the skin-sparing mastectomy, which involves removing the breast tissue through a circular incision around the nipple and replacing the breast with fat taken from the abdomen or back.

## ADJUVANT THERAPIES FOR BREAST CANCER

Radiation adjuvant therapy is routine after breast-conserving surgery (eg, lumpectomy) Table 5. Standard Adjuvant Chemotherapy Regimens Standard Regimens Components AC (w or w/o T) Adriamycin, cyclophosphamide, Taxol CMF Cyclophosphamide, methotrexate, fluorouracil (5-FU) CEF CAF Cyclophosphamide, epirubicin, fluorouracil (5-FU) Cyclophosphamide, adriamycin, fluorouracil (5-FU) to prevent recurrence of cancer in the breast, and it may be used after mastectomy to prevent recurrence on the chest wall and axilla. Radiation therapy is generally given 5 days a week over a 5- or 6-week time span, with care taken to try to avoid damage to the heart or lungs. The only usual changes with breast radiation are skin erythema and possibly some transient lymphedema.

Systemic adjuvant chemotherapy is never recommended for non-invasive, in situ cancer (DCIS). The most commonly used standard adjuvant chemotherapy regimens are listed in Table 5. Hormone adjuvant therapy helps to prevent recurrence by blocking the effects of estrogen, which is known to stimulate cancer cell growth. Hormones are most effective in women whose primary tumor has hormone receptors (ie, estrogen-receptor or progesterone-receptor positive). Tamoxifen is the standard first choice of most experts.<sup>84</sup> Other hormonal therapeutic agents include aromatase inhibitors, which interfere with the enzyme aromatase, which plays a critical role in the production of estrogen in postmenopausal women. Examples of this class include anastrozole, letrozole and exemestane.<sup>85,86</sup> A recent study of women who had completed 5 years of tamoxifen therapy and were assigned to either no therapy or continuing therapy with letrozole was prematurely ended when preliminary results revealed a greater than 40% reduction in recurrent breast cancers in the letrozole arm. Unanswered 96 RICHIE ET AL—BREAST CANCER questions are whether women should take letrozole for 5 years (the original study design) or indefinitely, and whether women should take letrozole (or one of the other aromatase inhibitors) instead of tamoxifen initially. [16].

An earlier head-to-head comparison of anastrozole and tamoxifen found that it was somewhat more effective in reducing the risk of a recurrence than tamoxifen.<sup>99</sup> Biological adjuvant therapy includes trastuzumab, which blocks the action of a growth-promoting protein called Her-2/neu that is found in larger-than-normal amounts in about 30% of breast cancers.<sup>87</sup> Trastuzumab more specifically targets cancer cells and thus has fewer side effects than standard chemotherapy, although it may have some effects on normal heart tissue when used with chemotherapy.<sup>88</sup> The drug has been approved for metastatic breast cancer and is currently under study as a first-line agent in combination with other chemotherapy.<sup>89</sup> PATTERNS OF RELAPSE The rate of local recurrence at 8 to 10 years has varied from 4% to 20%, with no differences between women who underwent

mas tectomy vs those who underwent breast-conserving therapy. However, the mortality implication of recurrence between the 2 groups is considerable. Women treated initially with breast-conservation therapy can present with locoregional recurrence in the preserved breast tissue. This may represent regrowth of the previous tumor or a second primary tumor. These patients can often be treated with mastectomy for curative intent. Women who have undergone a mastectomy as a primary treatment will usually manifest locoregional recurrence as a mass in the chest wall or overlying skin. This carries a much graver prognosis, since distant metastatic disease is already present in 25%–30% of these cases.<sup>90</sup> Breast cancer survivors are at increased risk for developing a second primary breast cancer compared with the general population (approximately 0.5% to 1% of women per year develop contralateral breast cancer).<sup>91</sup> Patients who have undergone breast cancer.

## Conclusion

Breast cancer remains a significant global health concern, impacting millions of individuals each year. This review has underscored the multifaceted nature of breast cancer, highlighting various risk factors and diagnostic approaches crucial in understanding and managing this disease. Moreover, advancements in diagnostic techniques have significantly improved early detection and treatment outcomes. Mammography, alongside emerging technologies like magnetic resonance imaging and molecular testing, plays a pivotal role in identifying breast cancer at its early stages, enabling prompt intervention and potentially improving patient prognoses. Moving forward, continued research into identifying additional risk factors, enhancing screening methods, and developing targeted therapies remains imperative. Furthermore, promoting awareness, advocating for increased screening accessibility, and fostering global collaboration among medical professionals and researchers is crucial in the ongoing fight against breast cancer. A comprehensive approach that integrates research, education, early detection, and accessible healthcare services is essential in combating breast cancer and reducing its impact on individuals and society worldwide.

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